The Case of the Missed Chest Radiograph

Bilateral Mammary Gland Metastases Mimicking Multifocal Primary Breast Cancer as the Initial Manifestation of Non–Small-Cell Lung Cancer

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A 53-year-old, postmenopausal, female never smoker of Caucasian descent, presented with a palpable mass in her left breast discovered during self-examination. She had not undergone screening mammography for the last 3 years before presentation and had no family history of breast or ovarian cancer. On palpation, the mass was solid and firmly attached to the thoracic wall. Mammography of the left breast indicated the presence of a multilobular mass measuring 3.1 × 2.8 cm in the lower-inner quadrant and a second, smaller lesion in the same quadrant measuring 1.1 × 1.2 cm (Fig. 1*A*, mediolateral oblique [MLO] mammography). Mammography of the right breast revealed the presence of a third lesion, measuring 1.3 × 0.9 cm in the upper-outer quadrant, (Fig. 1*B*,/MLO mammography). Despite the absence of spiculated margins and microcalcifications, all three lesions were labeled as Breast Imaging and Reporting Data System category 5 tumors. No enlarged axillar lymph nodes were observed during clinical and mammographic examination. No chest radiograph was performed at initial presentation. A subsequent ultrasound-guided biopsy of all three lesions revealed massive infiltration of the mammary gland by a poorly differentiated carcinoma comprising large and medium-size cells with hyperdense nuclei (Fig. 2*A*,*B*), that stained negative for mammoglobin, estrogen and progesterone receptors, but positive for thyroid transcription factor 1 (TTF1; Fig. 2*C*). The patient underwent computed tomography scan of the thorax that revealed the presence of a previously unidentified mass in the left lung that extended from the left apex to the left hilar region with lobular margins (Fig. 3*A*). The mass, that measured 9 × 9 × 6 cm, encapsulated the upper lobar branch of the left main pulmonary artery, restricting its lumen to 4 mm (Fig. 3*D*, long black arrows) and was in close proximity with the aortic arch, infiltrating the mediastinal pleura, the left subclavian artery, and the left oesophageal wall (Fig. 3*A*,*B*, short black arrows). Enlarged paratracheal, subcarinal, and left hilar lymph nodes were also noted (Fig. 3*B*, short black arrows). At the same time, multiple nodular lesions were observed in the left thoracic wall, in front of the major pectoralis muscle, with the largest one corresponding to the fixed breast mass that was reported as the presenting sign of the patient (Fig. 3*C*, white arrows). A subsequent computed tomography-guided biopsy of the thoracic mass confirmed the diagnosis of a poorly differentiated adenocarcinoma of the lung with a high mitotic index and a positive stain for TTF1. Morphological and immunohistochemical features of the breast lesions were consistent with metastases from the primary lung adenocarcinoma. Mutation analysis of the tumor specimen revealed no activating mutation of the *EGFR* gene and fluorescence in situ hybridization analysis with break-apart probes for the *ALK* gene was negative for the presence of an *ALK* rearrangement. On the basis of these findings, the patient received first-line chemotherapy encompassing paclitaxel carboplatin and bevacizumab. After three cycles of chemotherapy, reevaluation showed progressive disease in both the primary tumor and the metastatic lesions to the breast. The patient is currently receiving second-line chemotherapy with pemetrexed.

DISCUSSION

Mammary gland metastases from extramammary malignant neoplasms are rare, accounting for only approximately 2% of breast tumors.[1] The most common primary malignancy is a contralateral breast carcinoma, followed by leukemia and lymphoma.[1] Lung cancer represents a far less common tumor to metastasize to the breasts, with sporadic reports on lung adenocarcinoma[2,3] (one in a male patient),[3] large-cell neuroendocrine carcinoma,[3] squamous-cell carcinoma,[4] and small-cell lung cancer.[1,5] Moreover, in many cases, detection of metastases to the breast from solid tumors comes at a late clinical stage, when patients are already known to have systemic, widespread disease.[1] In the largest series reported to date, Hajdu et al.[1] described 51 patients with metastasis to the breast from various primary

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Disclosure: The authors declare no conflict of interest.
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DOI: 10.1097/JTO.0000000000000265

ISSN: 1556-0864/14/0911-1729

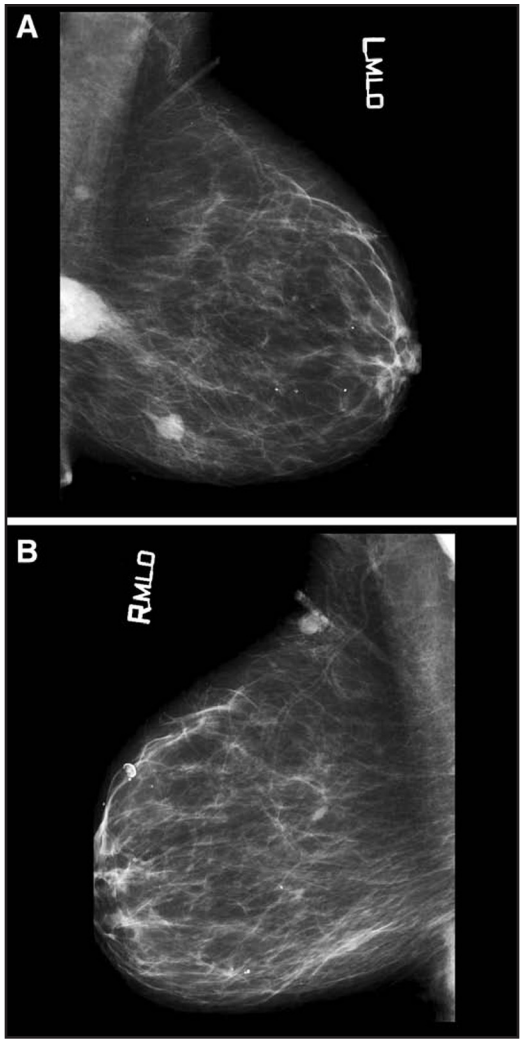

FIGURE 1. Mammographic images of the left (A) and right (B) breast. Mediolateral oblique view.

tumors over a period of 10 years, among which six patients with lung cancer (five with small-cell lung cancer and only one with non–small-cell lung cancer). Of note, the breast metastases were the first manifestation of disease in only 16 cases, including all six cases of lung cancer. To our knowledge, our case is the first one of confirmed bilateral mammary gland metastases that were the presenting sign of non–small-cell lung cancer. Our patient has chemoresistant disease, which confirms the dismal prognosis of patients with mammary gland metastases.[1] Despite being a never smoker, her tumor did not harbor any activating mutations in the *EGFR* gene or rearrangements of the ALK proto-oncogene. Future analysis will include testing for ROS1 or RET mutations in an effort to identify a driver genetic aberration in this patient.

Although on mammography metastatic lesions are usually characterized by multifocality and absence of axillar lymphadenopathy, as in our case, differential diagnosis between primary multifocal—or even bilateral—breast cancer and metastatic disease may prove challenging. In controversial cases, immunohistochemistry, and especially the use of the marker TTF1, allows a more confident differentiation between a primary breast

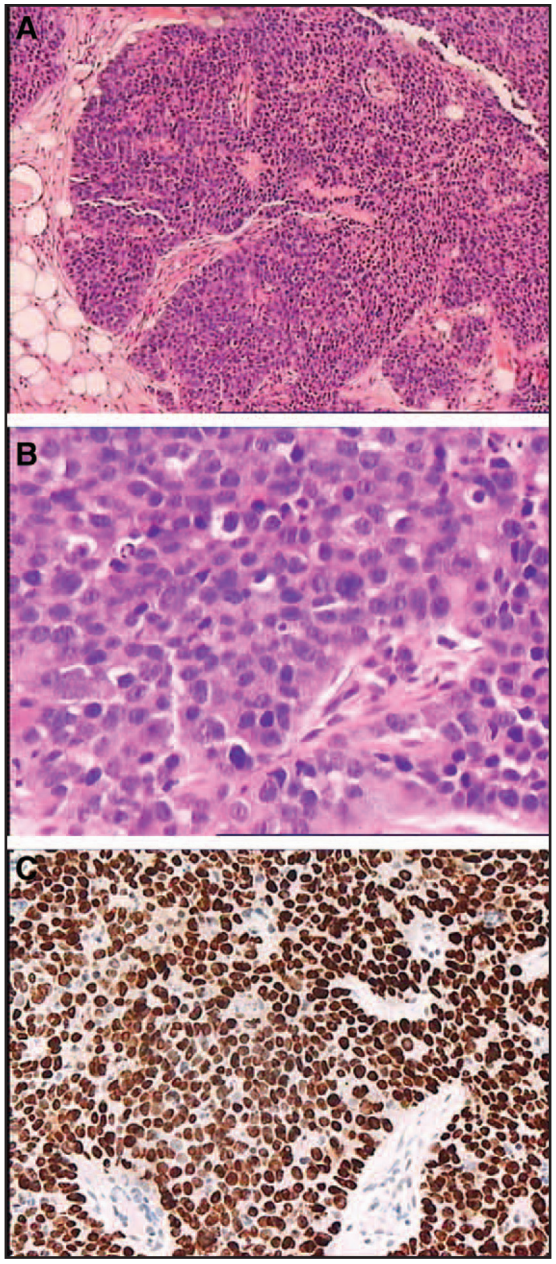

FIGURE 2. A and B, Hematoxylin-Eosin staining of the left breast tumor showing massive infiltration of the mammary gland by a poorly differenetiated carcinoma comprising medium and large-size cells with hyperdense nuclei (A, magnification X 10; B, magnification X 100). C, Strong positive staining of the tumor cells for thyroid transcription factor 1 (TTF1) (magnification X 40).

adenocarcinoma and metastasis from primary lung adenocarcinoma. To our knowledge, TTF1 positivity has never been described in primary breast tumors, whereas it represents a valid diagnostic marker for primary adenocarcinomas of the lung (specificity: 95–97%) and primary thyroid carcinomas.[1,2] For our analysis, we used the isotype IgG1 kappa monoclonal mouse antibody (Clone 8G7G3/1, Dako Pharmaceuticals), which identifies the 40 kDa TTF1 band in nuclear extracts or whole cell

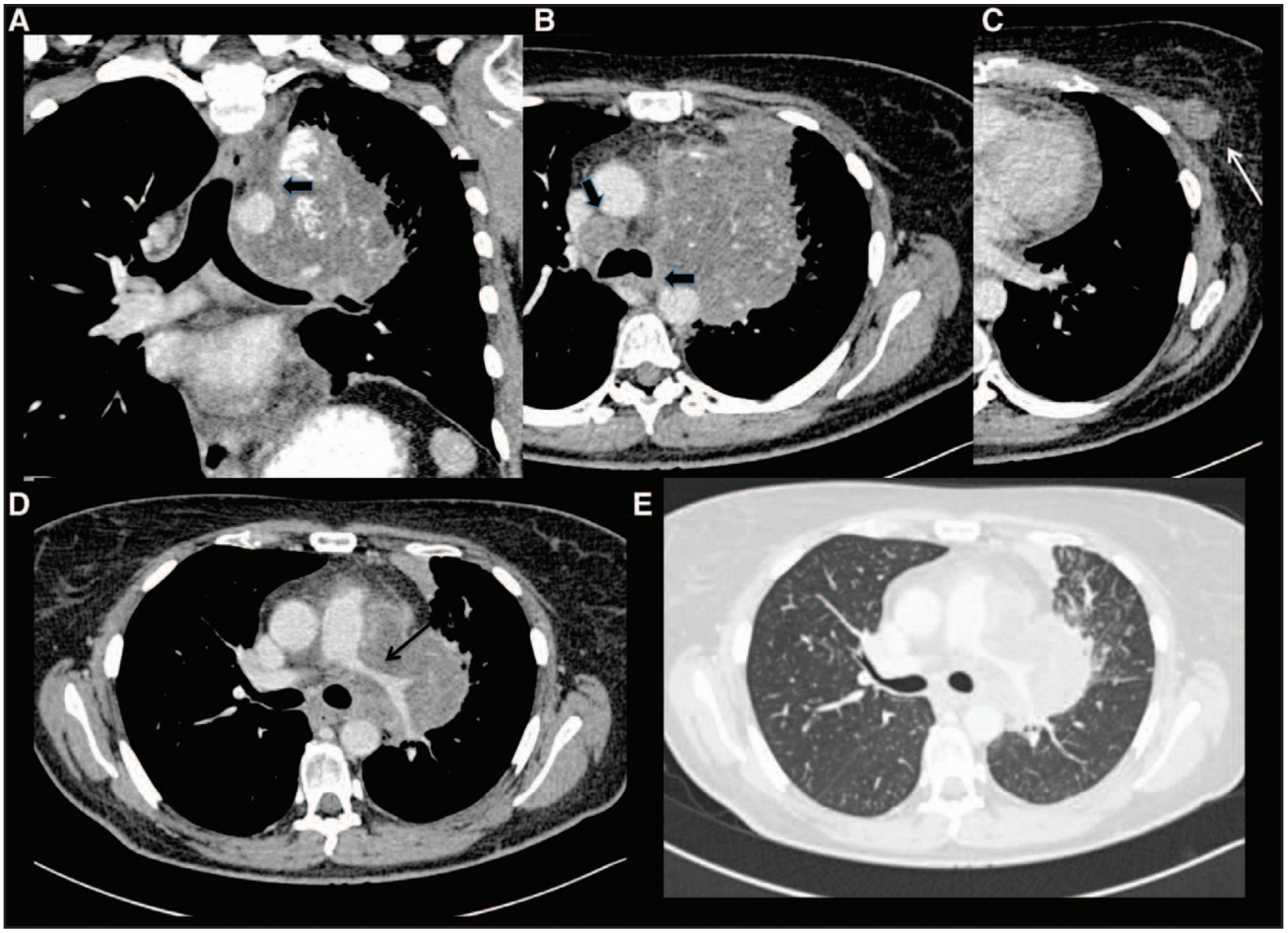

FIGURE 3. Computed tomography scan of the thorax showing the left lung mass extending from the left apex to the left hilar region with lobular margins (A, coronal axis), the enlarged paratracheal, subcarinal and left hilar lymph nodes (B, vertical axis), the left breast mass fixed on the left thoracic wall (C, vertical axis, white arrow), the encapsulation of the upper lobar branch of the left main pulmonary artery (D, vertical axis, long black arrow), and the same image in soft-tissue algorithm (E, vertical axis).

lysates of TTF1-positive cell lines of rat, mouse and man and is reported to demonstrate an excellent specificity.[6] TTF1 is not recommended for routine immunohistochemical testing of breast tumors. Nevertheless, in controversial cases, it can be used alongside with mammoglobin, hormone receptor and HER2/neu staining to determine the site of origin between the lung and the breast.

Although not routinely recommended as part of the diagnostic work-up of early breast cancer by the European Society for Medical Oncology guidelines,[7] radiograph of the thorax is included in the National Comprehensive Cancer Network guidelines[8] and remains an indispensable tool for the initial assessement in every patient with suspected malignancy, even in asymptomatic patients with nonsmoking history, as in our case. Although chest radiograph itself cannot safely differentiate between breast cancer metastatic to the lung and vice versa, radiologic evidence of a lung mass with mediastinal lymphadenopathy provides further support to the metastatic nature of breast lesions. Accurate diagnosis is of paramount importance, because it may obviate the need for unnecessary, extensive surgical procedures, which have little to offer in cases of widespread metastatic disease.

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